COMBINATIONS FOR DIABETES

CROSS-REFERENCE TO RELATED APPLICATION

This is a continuation-in-part of Ser. No. 08/970,057, filed Nov. 13, 1997, now U.S. Pat. No. 5,859,037, which claimed priority to U.S. provisional Ser. No. 60/038,224, filed Feb. 19, 1997.

FIELD OF THE INVENTION

This invention relates to combinations of antidiabetic compounds, and to a method for treating diabetes employing such combinations.

BACKGROUND OF THE INVENTION

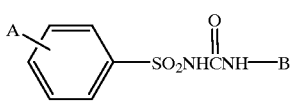
Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, insulin resistance, and is often associated with other disorders such as obesity, hypertension, hyperlipidemia, as well as complications such as cardiovascular disease, retinopathy, neuropathy, and nephropathy. The disease is progressive in nature, and can often be controlled initially by diet alone, but generally requires treatment with drugs such as sulfonylureas and injections of exogenous insulin. A new class of compounds known as the glitazones has recently received a great deal of attention for their ability to treat diabetes. These compounds operate by increasing the sensitivity of insulin receptors throughout the body, thereby diminishing or eliminating the need for exogenous insulin. Another agent known as a biguanide also is used to decrease hepatic glucose production as well as intestinal absorption of glucose.

It has now been discovered that combination therapy with a biguanide and a glitazone results in dramatic improvement in glycemic control, and that even better control can be achieved by using a combination comprised of a biguanide, a glitazone, and a sulfonylurea. Accordingly, such combinations are especially useful in treating diabetes and associated complications.

SUMMARY OF THE INVENTION

This invention provides a method of treating diabetes by administering to a subject in need of treatment a combination of a sulfonylurea antidiabetic agent and an antidiabetic glitazone, together with a biguanide antidiabetic agent such as metformin, or simply a glitazone together with a biguanide. The clinical data presented herein establishes the unexpected biological benefits achievable with these combinations.

The sulfonylureas are a class of compounds that have been widely employed to treat diabetes. Such compounds are well known, for example as described in U.S. Pat. Nos. 3,454,635, 3,669,966, 2,968,158, 3,501,495, 3,708,486, 3,668,215, 3,654,357, and 3,097,242. Most of the sulfonylurea antidiabetics are defined by the formula

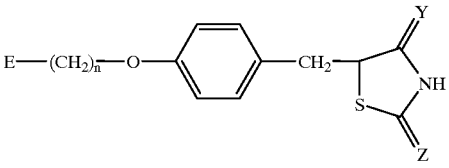


where A is hydrogen, halo, or an organic radical such as alkyl, alkanoyl, aryl, aralkyl, heteroaryl, and cycloalkyl, and B is alkyl, cycloalkyl, and a heterocyclic group such as hexahydroazepine. Preferred sulfonylureas to be employed are those wherein A is chloro, alkyl such as methyl, or alkyl

substituted with aryl carbonyl or aryl carboxamido, for instance 3-chloro-5-methoxybenzoylethyl or 5-methyl-2-pyrazinylcarbonylaminoethyl.

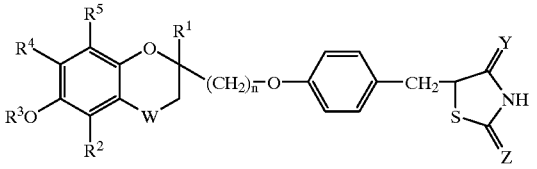
Especially preferred sulfonylureas to be employed in the combinations of this invention are glyburide, gliquidone, glipizide, tolbutamide, tolazamide, glisoxepid, chlorpropamide, glibornuride, gliclazide, glimepiride, phenbutamide, and tolcyclamide.

According to this invention, the foregoing sulfonylureas are used in combination with a glitazone to treat diabetes and to improve glycemic control. The glitazones are a family of antidiabetic agents characterized as being thiazolidinediones or related analogs. They are described in *Current Pharmaceutical Design*, 1996;2:85–101. Typical glitazones have the formula



where n is 1, 2, or 3, Y and Z independently are O or NH; and E is a cyclic or bicyclic aromatic or non-aromatic ring, optionally containing a heteroatom selected from oxygen or nitrogen.

Preferred glitazones have the formula



wherein:

R^1 and R^2 independently are hydrogen or C_1–C_5 alkyl;

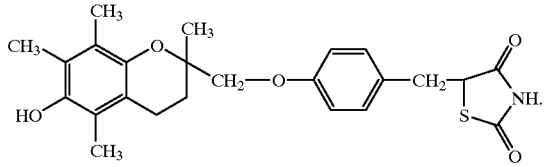
R^3 is hydrogen, a C_1–C_6 aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C_1–C_6 alkoxy) carbonyl group, or an aralkyloxycarbonyl group;

R^4 and R^5 independently are hydrogen, C_1–C_5 alkyl, C_1-C_5 alkoxy, or R^4 and R^5 together are C_1–C_4 alkylenedioxy;

W is —CH_2—, >CO, or CHOR^6, where R^6 is any one of the atoms or groups defined for R^3 and may be the same as or different from R^3;

n, Y, and Z are as defined above, and pharmaceutically acceptable salts thereof.

An especially preferred glitazone is troglitazone having the formula



Other glitazones that can be employed in this invention are described in U.S. Pat. No. 5,457,109, which is incorporated herein by reference. Other specific glitazones which